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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,622	05/07/2002	Nicholas Bachynsky	HO-P01615WO0	1907

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James J Napies  
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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/744,622

Applicant(s)

BACHYNSKY ET AL.

Examiner

Leslie A. Royds

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1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 May 2006; 06 July 2006; 31 August 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 100, 101 and 103-121 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 100-109, 111-117 and 119-121 is/are rejected.
- 7) ☒ Claim(s) 110 and 118 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 4/28/06; 08/14/06; 08/29/06
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

**Claims 100-101 and 103-121 are presented for examination.**

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and request filed May 25, 2006 have been received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant's response filed July 6, 2006 in response to the Notice of Non-Compliant Amendment dated June 6, 2006 has also been received and entered into the application. Additionally, Applicant's Supplemental Amendment filed August 31, 2006, in response to the Interview held August 17, 2006, has also been received and entered into the application.

Applicant's Information Disclosure Statements (IDS) filed April 28, 2006 (two pages), August 14, 2006 (one page) and August 29, 2006 (one page) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A (four pages total), the Examiner has considered the cited references except for the references cited as B1 and C28 on the IDS dated April 28, 2006. A reasonable search by the Examiner did not locate the references in the record. Accordingly, they have not been considered.

Claims 100-101 and 103-121 are pending and are under examination. Claim 102 has been cancelled and claims 100, 109 and 116 are amended.

Applicant's arguments, filed July 6, 2006, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

***Objections to the Claims (New Grounds of Objection)***

Claim 107 is objected to because the word "methotrexate" is misspelled as "metholtrexate" at line 2 of the claim.

Claims 100, 109 and 116 are objected to for reciting, "comprising the step of administering an amount of a mitochondrial uncoupling agent sufficient to the subject to induce whole body intracellular hyperthermia in the subject", which is grammatically awkward. Applicant may wish to consider amending the claims to read ---comprising the step of administering to the subject an amount of a mitochondrial uncoupling agent sufficient ~~to the subject~~ to induce whole body intracellular hyperthermia in the subject---.

Claims 110 and 118 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement***

***(New Grounds of Rejection)***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 100, 103-109, 111-117 and 119-121 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claims 100, 109 and 116 and the claims dependent therefrom are directed to a method for inducing intracellular hyperthermia in a subject comprising the step of administering an amount of a

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mitochondrial uncoupling agent sufficient to induce whole body intracellular hyperthermia in the subject, wherein the hyperthermia is used to treat cancers (i.e., prostate carcinoma, glioblastoma multiforme, Kaposi's sarcoma, peritoneal carcinoma or glioma), infections (i.e., *Borrelia burgdorferi*, *Mycobacterium leprae*, *Treponema pallidum*, HIV, hepatitis C, herpes virus or papillomavirus) or infestations (i.e., *Candida*, *Sporothrix schenckii*, *Histoplasma*, *Paracoccidioides*, *Aspergillus*, *Leishmania*, malaria, *acanthamoeba* or cestodes). Present claims 103, 111 and 119 specify that the mitochondrial uncoupling agent is a conjugate of 2,4-dinitrophenol.

In particular, the specification as originally filed fails to provide adequate written description for the claim limitations directed to (1) a mitochondrial uncoupling agent (claims 100, 109 and 116) or (2) a conjugate comprising 2,4-dinitrophenol (claims 103, 111 and 119).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in

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general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Present claims 100, 109 and 116 and the claims dependent therefrom recite the use of a “mitochondrial uncoupling agent” to induce intracellular hyperthermia. However, Applicant has failed to provide sufficient written description to support the genus of “mitochondrial uncoupling agents”. In fact, the present disclosure fails to recite any structural characteristics, chemical formula or physical properties that correlate to the compound’s function as a mitochondrial uncoupler that would provide adequate and limiting description of the mitochondrial uncoupling agents that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention.

Despite the fact that Applicant provides lists of compounds that are either “classic” uncoupling agents (i.e., those that act similarly to DNP), ionophorous antibiotics or a group of “heterogeneous compounds that dissipate the proton gradient by attaching or interacting with specific proteins in the inner mitochondrial membrane” (see pages 25-27 of the present specification), the lists are exemplary and fail to provide a limiting definition or any structural, chemical or physical characteristics of the mitochondrial uncoupling agents such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term “mitochondrial uncoupling agents”.

Although Applicant states that the mitochondrial uncoupling agents are capable of increasing intracellular heat and freeing radicals (see page 14 of the specification), such properties do not clearly and precisely point out those mitochondrial uncouplers of which Applicant was in possession at the time of the invention. While it may be construed that the fact that the agent must be capable of the function of mitochondrial uncoupling is sufficient to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, Applicant has failed to tie this functional property of the exemplary disclosed compounds to some sort of chemical or physical structure such that one of skill in the art would have been able to readily identify the compounds intended to be encompassed by the claims. In other words, the absence of any correlation between function and physical or chemical structure fails to provide an adequate

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description of the entire genus of compounds that fall within the genus of mitochondrial uncouplers. Furthermore, given the great variation in chemical structure, function and physical properties between each of the exemplified uncouplers present in the specification, one of skill in the art would have required additional direction and/or description as to what other compounds would be considered mitochondrial uncouplers, how such agents could be readily identified and whether such uncouplers would have been amenable for use in the claimed invention. In the absence of such description, Applicant's limitation to a "mitochondrial uncoupling agent" is not sufficiently supported by the present specification in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Regarding Applicant's limitation directed to "a conjugate of 2,4-dinitrophenol" (claims 103, 111 or 119), Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties that would provide adequate written description of the 2,4-dinitrophenol conjugates that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention.

Applicant's specification states, "Various conjugates, adducts, analogs and derivatives of the above mentioned agents can be formulated and synthesized to enhance intracellular uncoupling and heat production...Uncoupling-free radical prodrug compounds may thus exert greater selective killing of transformed cells by undergoing a higher flux of reduction or electron acceptance in tumor cells. In this regard, the contents of U.S. Patent NO. 5,428,163 and the published methods of C-alkylation of phenols and their derivatives by Hudgens, T.L. and Turnbull, K.D. are hereby incorporated by reference."

Such disclosure, while noted, provides only an exemplary and non-limiting teaching of what compounds would be considered within the scope of the term "conjugate of 2,4-dinitrophenol". Applicant has failed to provide any limiting definition or any structural, chemical or physical characteristics of these conjugate compounds such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "a conjugate of 2,4-

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dinitrophenol”.

While it may be construed that the fact that the compound is derived from or based upon the compound 2,4-dinitrophenol implies some sort of chemical or structural characteristic sufficient to fulfill the written description of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation or similarity that a compound may have from the parent compound 2,4-dinitrophenol and still be considered a conjugate for use as the mitochondrial uncoupling agent to induce intracellular hyperthermia. The mere fact that the only chemical or structural characteristic of the compound is that it is a conjugate of 2,4-dinitrophenol, wherein the degree of similarity or derivation from 2,4-dinitrophenol is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation to “a conjugate of 2,4-dinitrophenol” is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of (1) the genus of mitochondrial uncoupling agents or (2) conjugates of 2,4-dinitrophenol.

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

***Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.



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Claims 104-105, 112 and 120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 104, 112 and 120 are directed to a method for inducing intracellular hyperthermia for the treatment of, respectively, cancers (i.e., prostate carcinoma, glioblastoma multiforme, Kaposi's sarcoma, peritoneal carcinoma or glioma), infections (i.e., *Borrelia burgdorferi*, *Mycobacterium leprae*, *Treponema pallidum*, HIV, hepatitis C, herpes virus or papillomavirus) or infestations (i.e., *Candida*, *Sporothrix schenckii*, *Histoplasma*, *Paracoccidioides*, *Aspergillus*, *Leishmania*, malaria, *acanthamoeba* or cestodes), wherein an animal is administered the mitochondrial uncoupling agent and a separate medication, wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal or an increase in free radical flux.

First, it is unclear how the limitation "an animal" is intended to limit the parent claim from which it depends because each of independent claims 100, 109 or 116 recite the induction of intracellular hyperthermia in a subject. In other words, it is unclear whether the "an animal" is intended to be the same "subject" as presented in the independent claim, or whether it is intended to further limit the "subject" of the independent claim only to "an animal". Accordingly, the host intended to receive the intracellular hyperthermia cannot be readily identified by the claims as presently written and, therefore, the skilled artisan would not have been reasonably apprised of the scope of the subject matter for which Applicant is seeking protection.

Second, present claims 104, 112 and 120 require the administration of a separate medication with the mitochondrial uncoupling agent, but then state "wherein the second medication increases the overall metabolic rate of the animal, the metabolic rate of a specific target tissue in the animal or an increase in free radical flux". It is unclear whether "the second medication" is the same as the "a separate medication" referenced earlier in the claim or whether "the second medication" and the "a separate

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medication” are two distinct chemical entities. Accordingly, one of ordinary skill in the art would not have been reasonably apprised of the metes and bounds of the claimed subject matter.

Third, the limitation “the metabolic rate of a specific target tissue in the animal” does not clearly or expressly delineate what “target tissue” is affected by the second medication such that the skilled artisan would have been able to readily determine those medications that would have been included or excluded from the claim based upon this required function. Accordingly, one of ordinary skill in the art would not have been reasonably apprised of the scope of the subject matter for which Applicant is seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 105, 107, 115 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, it is noted that the claims recite the agents “methylene blue (tetramethylthionine)”, “etoposide (VP-16)”, “teniposide (VM-26)”, “vidarabine (ARA-A)”, “9-1,3-dihydroxy-2-propoxymethylguanine (DHPG)”, “2,3-dideoxytidine (ddQ)”, “iododeoxyuridine (IDU)”, “trifluorothymidine (TIFT)”, “dideoxyMosiine (ddi)”, “fluconazole (Diflucan)” or “5 fluoro-cytosine (Flutocytosine, 5-FC)”. The recitation of the parenthetical limitation(s) renders the scope of the claims indefinite because Applicant has failed to delineate how such limitations are intended to limit the claim. Though the limitations provided in the parentheses may be additional names that circumscribe the same compound, it is unclear whether the parenthetical recitation of these terms is intended to simply make reference to another known name for that same compound, or whether it is intended to limit the claim in another manner.

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For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and, thus, are properly rejected because the skilled artisan would not have been reasonably apprised of the scope of the claims.

***Claim Rejections - 35 USC § 102 (New Grounds of Rejection)***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 100, 101, 104, 105 and 106 are rejected under 35 U.S.C. 102(b) as being anticipated by Cone Jr. (U.S. Patent No. 4,724,234; 1988).

Cone Jr. teaches a method of producing oncolysis, i.e., lysis or degeneration or death of malignant cancer cells, by concurrent administration of two therapeutic regimens, wherein the first regimen is a defined nutritional regimen to minimize the use of amino acids and fatty acids as an energy source for ATP synthesis within the cancer cell(s), and further wherein the second regimen in the administration of 2,4-dinitrophenol in an amount sufficient to uncouple oxidative phosphorylation (col.7, line 51-co..8, line 5 and col.19, lines 26-39). Cone Jr. teaches the inclusion of the essential fatty acids linoleic and linolenic acids as part of the defined nutritional regimen (col.12, lines 8-19) and exemplifies the use of the disclosed regimen in patient(s) with retroperitoneal tumor mass (Example 3, col.28-31) and adenocarcinoma of the prostate (Example 4, col.31-34).

Though Cone Jr. does not expressly teach an intracellular hyperthermic effect via the induction of heat shock proteins as a result of the disclosed regimen, the administration of the same compound as claimed (i.e., 2,4-dinitrophenol with concurrent polyunsaturated fatty acids linoleic or linolenic acid) to cancerous cells (i.e., retroperitoneal or prostate) is considered to inherently have the claimed intracellular

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hyperthermic effect via the induction of heat shock proteins, whether expressly recognized by Cone Jr. or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

The explanation of an effect obtained when using a compound cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the intracellular hyperthermic effect via the induction of heat shock proteins was not itself recognized as a pharmacological effect of administering the 2,4-dinitrophenol in combination with a polyunsaturated fatty acid of Cone Jr. to patients suffering from retroperitoneal or prostate cancer, such an effect is not considered a new therapeutic application because the known treatment of retroperitoneal or prostate cancer using this combination of active agents was already known in the prior art. Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the fact that it may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

***Claim Rejections - 35 USC § 103 (New Grounds of Rejection)***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 100-101 and 104-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cone Jr. (U.S. Patent No. 4,724,234; 1988) in view of Pilepich et al. ("Androgen Deprivation with Radiation Therapy Compared with Radiation Therapy Alone for Locally Advanced Prostatic Carcinoma: A Randomized Comparative Trial of the Radiation Therapy Oncology Group", *Urology*, 45(4); 1995).

Cone Jr. teaches a method of producing oncolysis, i.e., lysis or degeneration or death of malignant cancer cells, by concurrent administration of two therapeutic regimens, wherein the first regimen is a defined nutritional regimen to minimize the use of amino acids and fatty acids as an energy source for ATP synthesis within the cancer cell(s), and further wherein the second regimen in the administration of 2,4-dinitrophenol in an amount sufficient to uncouple oxidative phosphorylation (col.7, line 51-co.8, line 5 and col.19, lines 26-39). Cone Jr. teaches the inclusion of the essential fatty acids linoleic and linolenic acids as part of the defined nutritional regimen (col.12, lines 8-19) and exemplifies the use of the disclosed regimen in patient(s) with retroperitoneal tumor mass (Example 3, col.28-31) and adenocarcinoma of the prostate (Example 4, col.31-34).

Though Cone Jr. does not expressly teach an intracellular hyperthermic effect via the induction of heat shock proteins as a result of the disclosed regimen, the administration of the same compound as claimed (i.e., 2,4-dinitrophenol with concurrent polyunsaturated fatty acids linoleic or linolenic acid) to cancerous cells (i.e., retroperitoneal or prostate) is considered to inherently have the claimed intracellular

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hyperthermic effect via the induction of heat shock proteins, whether expressly recognized by Cone Jr. or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

Though Cone Jr. does not expressly disclose the concomitant administration of an additional anticancer agent and/or radiation with the disclosed 2,4-dinitrophenol regimen, Pilepich et al. provides teachings that the administration of androgen deprivation therapy, using a combination chemotherapeutics such as goserelin and flutamide, before and during radiotherapy results in a marked increase in local control and disease-free survival of prostatic cancer patients compared with pelvic radiotherapy alone (see abstract at page 616).

One having ordinary skill in the art at the time of the present invention would have found it *prima facie* obvious to modify the method(s) disclosed by Cone Jr. to include concomitant administration of an additional anticancer agent (e.g., goserelin/flutamide) in addition to radiotherapy because each was known to have the same antitumor effects in prostate cancer patients. The very fact that each was known in the art to have the same therapeutic utility raises the reasonable expectation of success that such therapeutic modalities, when combined, would have, at minimum, additive, if not synergistic, antiproliferative effects when combined. Furthermore, the use of multiple therapeutic approaches (i.e., both chemotherapeutic and radiotherapeutic regimens) would have been reasonably expected to accommodate for the deficiencies in efficacy of single therapeutic modalities alone.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

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**Conclusion**

Applicant is invited to contact the undersigned Examiner to discuss the language of the claims and the rejections of record should Applicant feel that such an interview will help advance prosecution of the present application and clarify the issues set forth *supra*.

Rejection of claims 100-109, 111-117 and 119-121 is proper.

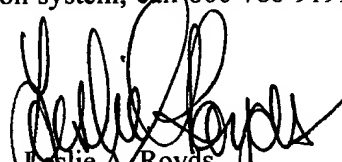
Claims 110 and 118 are objected to as being dependent upon a rejected base claim.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Leslie A. Royds  
Patent Examiner  
Art Unit 1614

November 8, 2006

  
ARDIN H. MARSCHEL  
SUPERVISORY PATENT EXAMINER

<b>Notice of References Cited</b>	Application/Control No. 09/744,622	Applicant(s)/Patent Under Reexamination BACHYNSKY ET AL.	
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**U.S. PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
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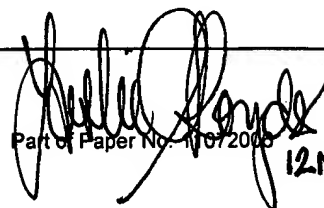
**FOREIGN PATENT DOCUMENTS**

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

**NON-PATENT DOCUMENTS**

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Pilepich et al. "Androgen deprivation therapy with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: A randomized comparative trial of the Radiation Therapy Oncology Group". Urology, 45(4); 1995:616-623.
	V	
	W	
	X	

\*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)  
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

  
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	2	Attorney Docket Number	HO-P01615US1
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## Complete if Known

Application Number	09/744,622
Filing Date	July 27, 1999
First Named Inventor	Nicholas Bachynsky
Art Unit	1614
Examiner Name	L. A. Royds
Attorney Docket Number	HO-P01615US1

## U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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LA2	A2	US-4,481,195	11-06-1984	Rubin	
LA2	A3	US-4,555,397	11-26-1985	Bachynsky	
LA2	A4	US-4,569,836	02-11-1986	Gordon	
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Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
LA2	B4	ALI-750313	07-18-2002	Bachynsky et al.		
LA2	B2	WO-97/35540	10-02-1997	Schick		

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<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See attached Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 801.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the application number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

## NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
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Examiner Signature	Date Considered	08 Nov 06
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PTO/SB/08A (10-01)

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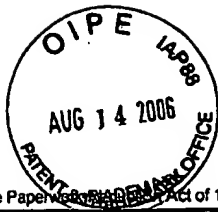
Substitute for form 1449A/PTO		<b>Complete if Known</b>	
		Application Number	09/744,622
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Filing Date	July 27, 1999
		First Named Inventor	Nicholas Bachynsky
		Art Unit	1614
		Examiner Name	L. A. Royds
		Attorney Docket Number	HO-P01615US1
Sheet	2	of	2

		Volume 1, 1867-1870, 2000.	
	C9	Dismukes, "Histoplasmosis," In: <i>Cecil Textbook of Medicine</i> , Goldman and Bennett, eds., 21st Edition, Volume 1, 1860-1862, 2000.	
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	C13	Erge et al., "Effects of Dinitrophenol on an Experimental Sarcoma of the White Rat," <i>Proc. Soc. Exper. Biol. Med.</i> , 31: 152-154, 1933.	
	C14	Feinberg, "Pneumocystis Carinii Pneumonia," In: <i>Cecil Textbook of Medicine</i> , Goldman and Bennett, eds., 21st Edition, Volume 1, 1877-1883.	
	C15	Galgiani, "Coccidioidomycosis," In: <i>Cecil Textbook of Medicine</i> , Goldman and Bennett, eds., 21st Edition, Volume 1, 1863-1864, 2000.	
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	C17	Karchmer, "Antibacterial Therapy," In: <i>Cecil Textbook of Medicine</i> , Goldman and Bennett, eds., 21st Edition, Volume 1, 1591-1603, 2000.	
	C18	Kumar, "Melatonin: a master hormone and a candidate for universal panacea," <i>Indian Journal of Experimental Biology</i> , 34(5): 391-402, 1996.	
	C19	Lock et al., "Differential Ability of 2, 4-Dinitrophenol to Modulate Etoposide Cytotoxicity in Mammalian Tumor Cell Lines Associated with Inhibition of Macromolecular Synthesis," <i>International Journal of Oncology</i> , 8(2): 305-311, 1996.	
	C20	Nozue et al., "Effect of Some Enzyme Inhibitors on ATP Level and Hypersensitive Reactivity of Potato Tuber Disks to Incompatible Race of <i>Phytophthora infestans</i> ," <i>Nippon Shokubutsu Byori Gakkaiho - Annals of the Phytopathological Society of Japan</i> , 46(1): 34-39, 1980.	
	C21	Oda et al., "The Effect of Induced Hyperthermia on Kidney Function in Dogs," <i>Japanese Journal of Anesthesiology</i> , 35(9): 1374-1379, 1986.	
	C22	Oka et al., "Immunosuppression in organ transplantation," <i>Japanese Journal of Pharmacology</i> , 71(2): 89-100, 1996.	
	C23	Rickels et al., "The clinical presentation of generalized anxiety in primary-care settings: practical concepts of classification and management," <i>J. Clin. Psychiatry</i> , 58(Suppl. 11): 4-10, 1997.	
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	C26	Smith et al., "Hormone replacement therapy in the menopause: a pro opinion," <i>CA Cancer J. Clin.</i> , 46(6): 343-63, 1996.	
	C27	Sri-Pathmanathan et al., "Clofazimine Alters the Energy Metabolism and Inhibits the Growth Rate of a Human Lung-Cancer Cell Line In Vitro and In Vivo," <i>International Journal of Cancer</i> , 56(6): 900-905, 1994.	
	C28	Stevens, "Aspergillosis," In: <i>Cecil Textbook of Medicine</i> , Goldman and Bennett, eds., 21st Edition, Volume 1, 1875-1883, 2000.	

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	08 November 2002
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			Application Number	09/744,622	
			Filing Date	July 27, 1999	
			First Named Inventor	Nicholas Bachynsky	
			Art Unit	1614	
			Examiner Name	L. A. Royds	
Sheet	1	of	1	Attorney Docket Number	HO-P01615US1

U.S. PATENT DOCUMENTS					
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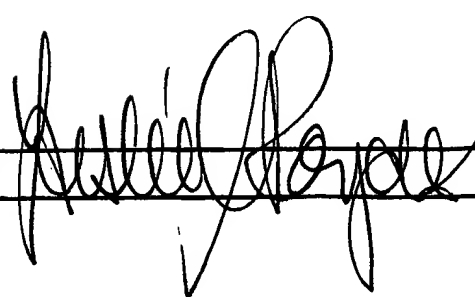
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<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See attached Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the application number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

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NAL	CA	Weitzel et al., "Similar Dose Response of Heat Shock Protein Synthesis and Intracellular pH Change in Yeast," <i>Exp. Cell. Res.</i> , 159: 252-256, 1985.	

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Examiner Signature		Date Considered	08 NOVEMBER 2000
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Sheet	1	of	1	Attorney Docket Number	HO-P01615US1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>

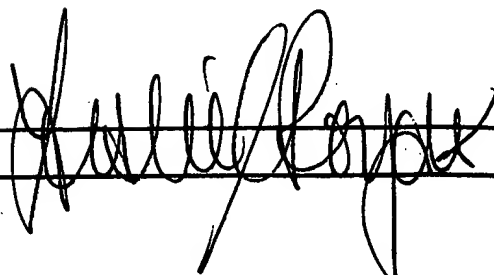
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LA	C1	European Search Report for EP 99 93 5949, issued 15 July 2003.	
LA	C2	Summons to attend oral proceedings pursuant to Rule 71(1) EPC for EP 99 93 5949, issued 6 April 2006.	

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<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	08 NOV 2006
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## ANDROGEN DEPRIVATION WITH RADIATION THERAPY COMPARED WITH RADIATION THERAPY ALONE FOR LOCALLY ADVANCED PROSTATIC CARCINOMA: A RANDOMIZED COMPARATIVE TRIAL OF THE RADIATION THERAPY ONCOLOGY GROUP\*

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JOHN M. KRALL, Ph.D.      COLLEEN A. LAWTON, M.D.      DAVID GRIGNON, M.D.  
MUHYI AL-SARRAF, M.D.      ROSS A. ABRAMS, M.D.      RICHARD CAPLAN, Ph.D.  
MADHU J. JOHN, M.D.      MARVIN ROTMAN, M.D.      JAMES D. COX, M.D.  
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**ABSTRACT—Objectives.** Androgen deprivation therapy before and during radiation therapy could, by reducing tumor volume, increase local tumor control, disease-free survival, and overall survival in patients with locally advanced adenocarcinomas of the prostate.

**Methods.** In a randomized controlled clinical trial, patients with large T2, T3, and T4 prostate tumors, but no evidence of osseous metastasis, were randomized to receive goserelin 3.6 mg subcutaneously every 4 weeks and flutamide 250 mg orally three times daily 2 months before and during the radiation therapy course (Arm I) compared with radiation therapy alone (Arm II). Pelvic irradiation was administered with 1.8 to 2.0 Gy per day to a total dose of  $45 \pm 1$  Gy followed by a boost to the prostate target volume to a total dose of 65 to 70 Gy.

**Results.** Of 471 randomized patients, 456 were evaluable, 226 on Arm I and 230 on Arm II. With a median potential follow-up of 4.5 years, the cumulative incidence of local progression at 5 years was 46% in Arm I and 71% in Arm II ( $P < 0.001$ ). The 5-year incidence of distant metastasis on Arms I and II was 34% and 41%, respectively ( $P = 0.09$ ). Progression-free survival rates including normal prostate-specific antigen (PSA) levels for 396 patients with at least one PSA recorded were 36% in Arm I and 15% in Arm II at 5 years ( $P < 0.001$ ). At this time, no significant difference in overall survival could be detected ( $P = 0.7$ ).

**Conclusions.** Short-term androgen deprivation with radiation therapy results in a marked increase in local control and disease-free survival compared with pelvic irradiation alone in patients with locally advanced carcinoma of the prostate. Long-term surveillance is required to assess effects on overall survival.

\*Supported by Public Health Service grants CA-21661 and CA-32115 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.  
Submitted (Rapid Communication): September 29, 1994;  
accepted (with revisions): January 5, 1995

Radiation therapy is a well-established modality in the curative management of carcinoma of the prostate. In patients with small tumors and no evidence of spread beyond the pelvis, external beam irradiation has been associated with high locoregional

control rates and long-term survival rates comparable to those achieved with radical surgery.<sup>1</sup> The probability of locoregional recurrence, however, increases with increasing size of the primary tumor as reflected in T stage.<sup>2</sup> Despite the subjectivity and lesser accuracy than transrectal ultrasonography, large tumor size defined by the product of palpable tumor dimensions in centimeters at digital rectal examination, correlated strongly, even within stage, with locoregional failure in patients treated on prior studies of the Radiation Therapy Oncology Group (RTOG).<sup>3</sup> More than 50% of patients in whom the product of tumor dimensions exceeded 25 cm<sup>2</sup> had locoregional failure by the sixth year after completion of treatment.<sup>4</sup>

Androgen deprivation therapy in patients with disseminated carcinoma of the prostate is associated with a high response rate. The traditional methods of androgen deprivation include orchiectomy and estrogen administration. Newer approaches consist of administration of luteinizing hormone-releasing hormone (LHRH) agonists and androgen receptor blockers.

Investigators of the RTOG have studied the potential value of androgen deprivation therapy as an adjuvant to definitive radiation therapy since the early 1980s. One of the tested treatment regimens<sup>5</sup> used androgen deprivation therapy prior to and during irradiation, based on the hypothesis that reduction in the tumor volume prior to radiation therapy could lead to increased control of the primary tumor at a specific level of radiation dose. Current concepts of apoptotic regressions associated with reductions of dihydrotestosterone<sup>6</sup> suggest that adjuvant androgen deprivation could enhance the cell killing of radiation therapy. Early RTOG studies of hormonal cytorreduction via androgen deprivation established the tolerance of short-term hormonal alterations in regard to acute reactions from pelvic irradiation and the preservation of potency postirradiation.<sup>5,7</sup> A Phase III trial was developed to compare standard radiation therapy alone with short-term use of an LHRH analogue plus an androgen receptor blocking agent before and during radiation therapy.

#### MATERIAL AND METHODS

The study was designed to test the potential value of a combination of goserelin acetate, an LHRH analogue, and flutamide, an antiandrogen, used as cytorreductive agents prior to and during radiation therapy in locally advanced (bulky) carcinoma of the prostate without radionuclide evidence of osseous metastasis. Patients on the control arm received radiation therapy only.

The endpoints of the study included local control rates, progression-free survival, and survival. The primary endpoint was the local control rate. Although the study was designed before prostate-specific antigen (PSA) determinations were available, their widespread use for determining outcome mandated their consideration in the analysis.<sup>8-12</sup>

#### ELIGIBILITY AND STUDY DESIGN

The criterion for enrollment was histologic evidence of adenocarcinoma of the prostate, either confined to the prostate (clinical Stage T2b, T2c, or B2)<sup>13</sup> or extending beyond the capsule (clinical Stage T3, T4, or C), with no evidence of dissemination beyond regional lymph nodes. The tumors were required to be 25 cm<sup>2</sup> or more as measured by the surface area palpable by digital rectal examination. Patients with regional lymph nodes were eligible provided the involved nodes were below the common iliac chain. Patients with involved common iliac or periaortic lymph node involvement were not eligible. The lymph node evaluation was carried out by either computed tomography (CT), lymphography, or lymphadenectomy. Karnofsky performance status<sup>14</sup> had to be equal to or greater than 60. Pretreatment evaluation included medical history, including sexual function, and physical examination. The required studies included chest roentgenograms and radionuclide bone scans, complete blood count (CBC), serum aspartate transaminase, and alanine transaminase (only on patients who were to receive goserelin and flutamide). Serum prostatic acid phosphatase (PAP) and testosterone levels were mandatory for all patients. During the early years of the study, PSA was not available, but the protocol was later revised to include PSA determinations.

The study protocol was approved by the National Institutes of Health, the review boards of the RTOG, and all the participating institutions. All the patients gave informed written consent before they were enrolled.

The randomization scheme described by Zelen<sup>15</sup> was used to achieve balance among the institutions, with two stratification variables: clinical Stage (T2, T3-4) and histopathologic differentiation (well, moderate, poor).

#### TECHNIQUES OF TREATMENT

##### RADIATION THERAPY

Megavoltage radiation therapy units were used with a minimal distance of 80 cm from the source to the axis of treatment. Patients with no evidence of tumor spread to the pelvic lymphatic system were treated to a target volume that extended up

TABLE I. Pretreatment characteristics

	All Patients		Patients With One or More PSA Reading	
	Goserelin + Flutamide + Radiation Therapy (n = 226)	Radiation Therapy Alone (n = 230)	Goserelin + Flutamide + Radiation Therapy (n = 196)	Radiation Therapy Alone (n = 200)
Age				
Median	70	71	70	71
Range	50-88	49-84	53-88	49-84
Performance status (KPS)				
100	87 (38%)	96 (42%)		
90	121 (54%)	124 (54%)		
80	15 (7%)	10 (4%)		
70	2 (1%)	0 (0%)		
60	1 (<1%)	0 (0%)		
Differentiation				
Grade 1	34 (15%)	35 (15%)	31 (16%)	30 (15%)
Grade 2	84 (37%)	80 (35%)	75 (38%)	70 (35%)
Grade 3	63 (28%)	78 (34%)	55 (28%)	69 (35%)
Grade 4	29 (13%)	20 (9%)	21 (11%)	16 (8%)
Unknown/missing	16 (7%)	17 (7%)	14 (7%)	15 (8%)
Gleason score				
2-5	33 (15%)	34 (15%)	31 (16%)	30 (15%)
6-7	131 (58%)	123 (53%)	112 (57%)	109 (55%)
8-10	59 (26%)	69 (30%)	51 (26%)	57 (29%)
Missing	3 (1%)	4 (2%)	2 (1%)	4 (2%)
Nodal status				
Positive	16 (7%)	21 (9%)	14 (7%)	19 (10%)
Negative	207 (92%)	209 (91%)	179 (91%)	181 (91%)
Missing	3 (1%)	0 (0%)	3 (2%)	0 (0%)
Serum acid phosphatase				
Normal	130 (58%)	126 (55%)	115 (59%)	105 (53%)
Abnormal	87 (38%)	87 (38%)	74 (38%)	81 (41%)
Unknown	9 (4%)	17 (7%)	7 (4%)	14 (7%)
Clinical stage				
T2 (B2)	67 (30%)	70 (30%)	61 (31%)	59 (30%)
T3-4 (C)	159 (70%)	160 (70%)	135 (69%)	141 (71%)

bone metastasis (1), and benign disease (1). As of April, 1994, the median potential follow-up was 4.5 years and the median period of observation was 3.3 years (mean, 3.4 years).

Pretreatment prognostic factors are well-balanced between the two groups (Table I). Of the 37 (8.1%) patients considered to have pelvic lymph node metastasis, 23 had histologic confirmation and 14 had abnormal CT scans. There was no interaction between treatments and any of the prognostic factors, that is, treatment effect was similar in each of these subgroups: grade, Gleason score, stage, and initial PAP level. Of the 225 patients in Arm I with compliance information, 211 (94%) completed goserelin treatment and 188 (84%) completed flutamide treatment as planned. Treatment was terminated for flutamide toxicity in 23 patients. Reasons for termination were diarrhea (11), hot

flushes (3), liver function abnormalities (3), and other various reasons (rash, nausea, syncope). Two patients refused goserelin, 1 of whom also refused flutamide, but they are included in analyses. Thus, 186 patients completed both goserelin and flutamide treatment as planned.

No patient was reported to have acute grade 4 or 5 toxicities from radiation therapy. Three patients were reported with grade 4 toxicities in follow-up, 1 with hematuria in Arm I and 1 each with hematuria and hematochezia in Arm II. Grade 3 toxicities were reported in 7.1% (16/226) and 7.4% (17/230) of patients in Arms I and II, respectively.

There was no difference in frequency or time of return of sexual potency in the treatment groups; 81 of 102 of the radiation therapy plus hormone group and 74 of 102 of the radiation therapy alone group reported return of sexual function

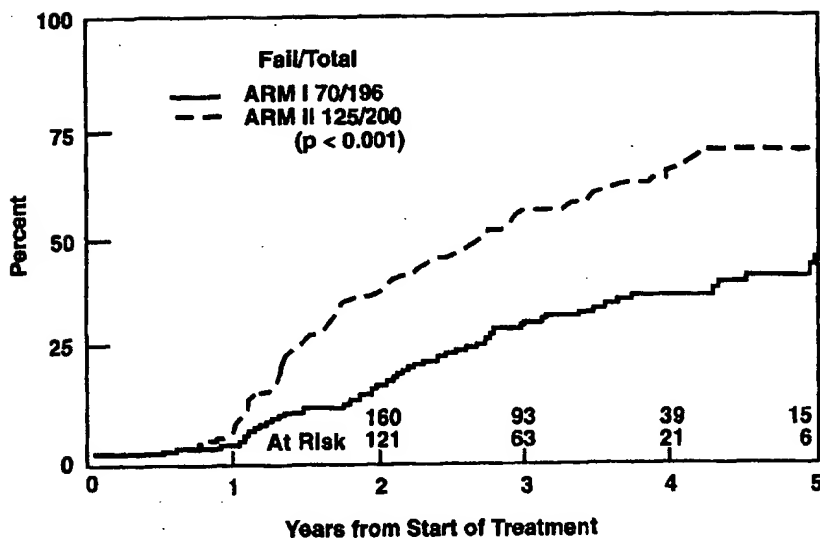


FIGURE 1. Cumulative incidence of local progression by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

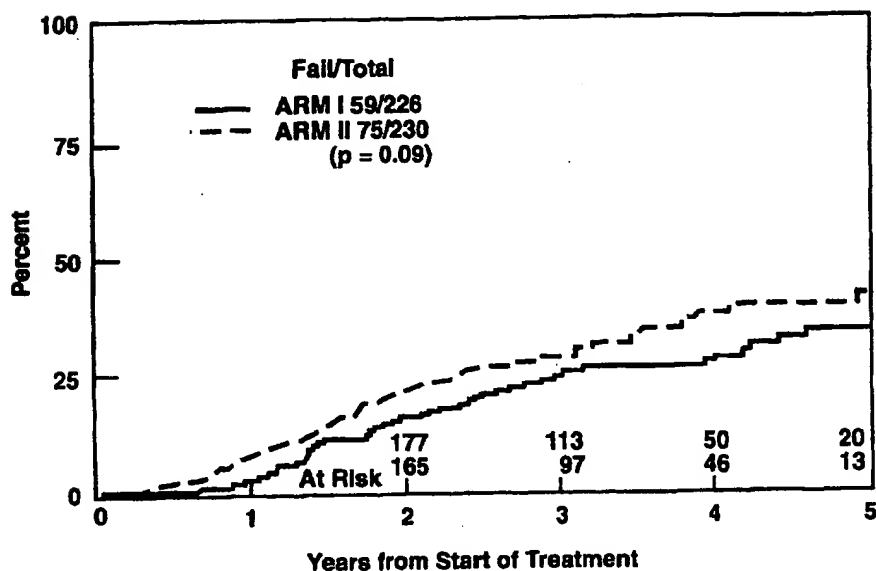


FIGURE 2. Cumulative incidence of distant metastasis by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

(denominator in each group was number of patients reporting potency at time of enrollment). There was no difference between the treatment groups in respect to development of second primary malignant tumors; 9 of the radiation therapy plus hormone treatment group and 11 of the radiation therapy alone developed second primaries.

Biopsy result alone was the only evidence of failure in 1 patient; all other patients with positive biopsy results either had rising PSA or clinical progression. Of the patients who had biopsies taken more than 2 years, 8 of 19 (42%) in the radiation therapy plus hormone group and 11 of 19 (58%) in the radiation therapy alone group had positive biopsy results.

A subset of the study cohort was used for the analysis of progression-free survival and local progression consisting of patients with at least one PSA level recorded. The total subset size was 396, with 196 and 200 patients in Arm I and Arm II, respectively. Among patients included in the analysis of progression, the median time from the end of radiation therapy to the first PSA measurement was 9.6 months. After the first PSA measurement, patients had an average of 2.1 PSA determinations per year until progression, death, or last event-free follow-up visit.

There was a significant decrease in local progression for patients in Arm I (Fig. 1) ( $P < 0.001$ ): 70 treated patients versus 125 control patients



to L5-S1 interspace. In patients with evidence of pelvic lymph node involvement, the superior border was extended to include the lower para-aortic lymph nodes to the level of the L2-L3 interspace. The inferior margin of the field was at or immediately above the ischial tuberosity. The lateral margins were 1 cm lateral to the maximum width of the bony pelvis. A "boost" target volume included the prostate with margins sufficiently wide to encompass all of the tumor extensions into the surrounding tissues. Multiple fields were used to limit the total dose to the surrounding normal tissues. The large field, including the regional lymphatics, received a minimum total dose of  $45 \pm 1$  Gy. The small boost volume received an additional 20 to 25 Gy, bringing the minimum total dose to the tumor-containing volume from 65 to 70 Gy. The daily doses were 1.8 to 2.0 Gy, 5 days per week.

#### HORMONE THERAPY

Goserelin acetate (Zoladex), 3.6 mg, was administered subcutaneously every 4 weeks starting 2 months prior to initiation of radiotherapy. It was continued during radiation therapy for a total of four injections. Flutamide (Eulexin), 250 mg orally three times daily was also started 2 months prior to initiation of radiotherapy and was continued throughout the radiotherapy course.

A central review of the radiation therapy delivered for each case was performed by the study chair. The calibration of every machine on which a patient was treated was obtained from the Radiologic Physics Center at The University of Texas M.D. Anderson Cancer Center. Individual treatment parameters, such as total dose, field borders, and elapsed treatment days, were reviewed relative to protocol specifications. Report forms for compliance with drug administration were reviewed by headquarters staff and the study chair.

Radiation-induced effects on normal tissue<sup>16</sup> were assessed as either acute or late phenomena. Toxicity related to treatment was considered to be acute if it occurred within the first 90 days from the start of treatment. Toxicity was considered to be late if it occurred after 90 days or an acute toxicity persisted beyond day 90. The toxicities were scored from 0 (none) to 5 (fatal), with grades 3, 4, and 5 considered as major.

Central review of materials on which the diagnosis was based was performed for consistency in assigning degree of differentiation and Gleason scores. If central review data were not available, interpretations by the institutional pathologist were used.

#### DATA COLLECTION AND STATISTICAL ANALYSIS

Local progression was defined as a PSA level more than 4 at 1 year or more from randomization or additional hormonal therapy in the absence of metastatic disease, an increase of more than 50% in tumor size (cross-sectional area), recurrence of a palpable tumor after initial clearance, or biopsy specimen revealing adenocarcinoma of the prostate 2 years or more after study entry. Regional metastasis was defined as clinical or radiographic evidence of tumor in the pelvis with or without palpable tumor in the prostate by digital rectal examination. Distant metastasis was defined as clinical or radiographic evidence of disease beyond the pelvis. A failure in progression-free survival is defined as a failure in either survival, local progression, or regional or distant metastasis.

Survival was measured from the date of randomization to the date of death or the most recent follow-up. Time to a distant metastasis or a local progression (after reported tumor clearance by palpation) was measured from the date of randomization to the occurrence of either event or to the date of the most recent follow-up. Progression-free survival was measured from the date of randomization to the earliest occurrence of either death, local progression, or metastasis or to the date of the most recent follow-up. Estimates of survival and progression-free survival were derived by the Kaplan-Meier<sup>17</sup> method. The cumulative incidence of local progression and metastasis was estimated.<sup>18</sup> Statistical comparisons for survival and progression-free survival were made by the log-rank statistic in the case of censored data or by the proportional-hazards analysis to control for prognostic factors. Statistical comparisons for the cumulative incidence of local progression or distant metastases were made using Gray's test.<sup>19</sup> All the statistical comparisons were made with two-tailed tests. Assessment of sexual functions was based on patients' answers to the question, "Able to have an erection? No, Yes, or Unknown," which was ascertained at baseline and at every follow-up visit.

#### RESULTS

From April 15, 1987, through June 1, 1991, when the study was closed, 471 patients were enrolled. Central pathology review was completed for 98% (461 of 471) of the patients. Fifteen patients were excluded, leaving 456 analyzable patients, 226 on the treatment and 230 on the control arm. The reasons for exclusion were no follow-up (4), tumor too small (5), refused all treatment and follow-up (3), lung primary (1),

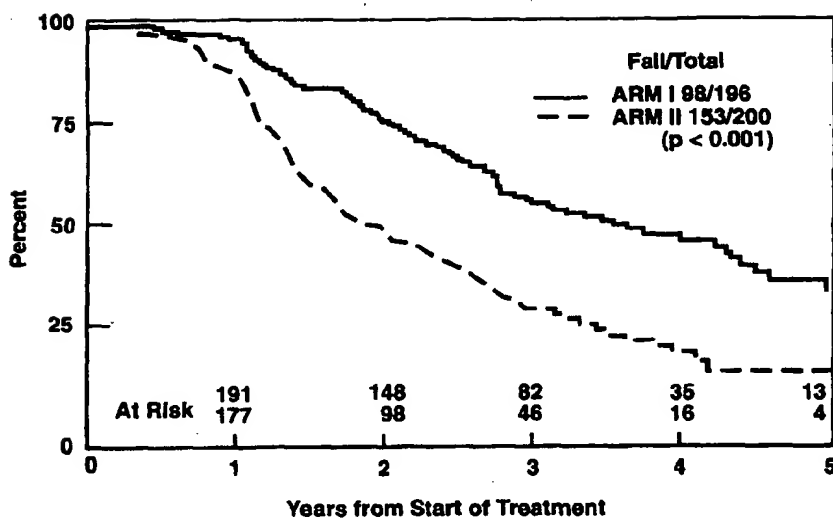


FIGURE 3. Progression-free survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

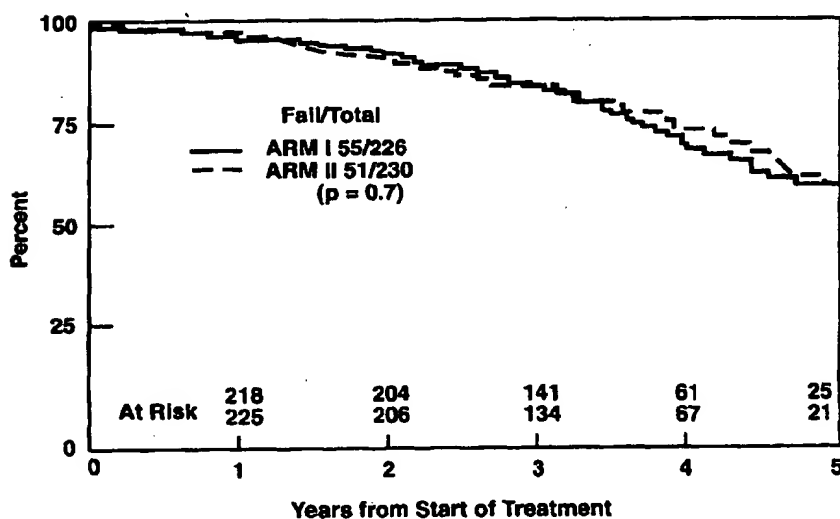


FIGURE 4. Survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

had local progression. The 5-year cumulative incidence of local progression was 46% on Arm I and 71% on Arm II, respectively. A decrease in the incidence of metastasis was observed for patients in Arm I (Fig. 2) ( $P = 0.09$ ): 59 treated patients developed metastasis compared with 75 control patients. The 5-year incidence of metastasis was 34% in Arm I and 41% in Arm II. There was a significant improvement in progression-free survival for patients in Arm I (Fig. 3) ( $P < 0.001$ ) (5-year rates of 36% for Arm I, 15% for Arm II). There was no significant difference in survival between the two treatment groups ( $P = 0.7$ ) (Fig. 4).

#### COMMENT

Radiation therapy has for 3 decades been considered one of the gold standards of treatment for both early and locally advanced prostatic carcinoma. In recent years, the long-term success of

both radiation therapy and radical surgery has come under significant challenge with the use of more stringent criteria for local control and for relapse-free existence. For instance, a number of series have been published in which a biopsy of the prostate glands was redone 18 months or more following irradiation.<sup>20-23</sup> Although in none of these series was it clear that the patients selected to have a re-biopsy were in any way representative of the entire irradiated population, it is disquieting that in these series from 18% to 90% of re-biopsy specimens showed viable tumor.

The likelihood of obtaining a positive re-biopsy is low when the serum PSA is low, but it is more than 80% when PSA is elevated following treatment. This is consistent with the now wide use of serum PSA to detect persistent or recurrent disease.<sup>10,11,24</sup> These data show that recurrence-free survival figures are approximately 20% worse

when using an abnormal serum PSA as a definition of recurrence compared with those obtained historically using purely clinical endpoints. With the use of these two new yardsticks, pathologic local control and a serum PSA in the normal range as tumor control endpoints, it is evident that both radiation therapy<sup>10,21</sup> and surgery<sup>12</sup> are considerably less effective than was previously presumed.

The RTOG randomized trial that is reported here has tested one of the important strategies available to oncologists in urologic cancer to improve local control, namely, an attempt to reduce the tumor volume prior to irradiation, which, if it is accompanied by a decrease in the number of tumor clonogens, should improve local cure. This strategy has the advantage of not requiring radiation dose escalation with the attendant risks of morbidity. The goal is to reduce safely local recurrence, which is accompanied by substantial local morbidity<sup>25</sup> and possibly by a second wave of metastases.<sup>26</sup>

Androgen dependence of human prostate carcinoma was first observed by Huggins and Hodges in 1941<sup>27</sup> with the cytotoxic effect of androgen suppression recently becoming understood as genetically controlled apoptosis.<sup>6</sup> The possible long-term benefits of androgen deprivation by both an LHRH analogue and an androgen receptor blocker that we report here have recently been shown to be of survival benefit in men with minimal bony metastatic disease.<sup>28</sup>

The patients enrolled in this study had the most advanced carcinoma of the prostate still treated with curative intent: 70% were classified as T3 or T4 and could extend from one pelvic side wall to the other. Even the 30% with T2b-c tumors had a minimum size by palpation of 5 by 5 cm. Approximately 40% of the patients had elevated PAP levels. In the group treated with radiation alone, almost two thirds of the patients are estimated to be alive at 5 years. A 4-month course of goserelin and flutamide (costing \$2168 to the pharmacist)<sup>29</sup> before and during radiation therapy, markedly reduced the incidence of treatment failures with no increase in major toxicity. A relationship has been shown between control of the tumor in the prostate by radiation therapy and a decreased risk of metastasis.<sup>26,30</sup> If this is confirmed in long-term observations of the men included in this study, an eventual survival benefit would be expected. It may take several additional years of observation to assess the effect of this brief hormonal treatment on overall survival. In the interim, the individual patient and his physician will have to weigh the cost of the treatment with the potential for in-

creased months and years free of new manifestations of prostate cancer.

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#### EDITORIAL COMMENT

I am pleased that the RTOG chose to publish the results of this prospective randomized trial in *Urology* for several reasons. First, urologists, in general, have the perception that radiation therapy is of limited value in the treatment of Stages T1-T3 prostate cancer. Second, we realize the importance of performing a properly conducted trial to answer therapeutic questions and, I believe, are likely to adopt the conclusions of such a study.

Realizing the relatively poor progression-free survival with radiation therapy alone in clinical T2b-T4 prostate cancer, the RTOG embarked on a study to evaluate the efficacy of the luteinizing hormone-releasing hormone analogue goserelin in combination with flutamide for 2 months before and 2 months during radiation therapy in an attempt to improve local control and both progression-free as well as overall survival. At a median potential follow-up of 4.5 years, patients not receiving androgen deprivation had a significantly greater incidence of local progression (71% versus 46%) and a lower progression-free survival (15% versus 36%). Importantly, the definition of progression-free survival included a PSA level of 4 or less.

Was the study perfect? Of course not. A few concerns are:

1. All patients did not have a PSA performed, since its importance as an indicator of tumor control was not fully appreciated in 1987 when the study was initiated.
2. A PSA level of 4 is probably too high to use as the upper limit of normal following radiation therapy.
3. Few patients had a biopsy done and thus the rectal examination (and PSA) were the primary criteria for local control. We know all too well how inaccurate the digital rectal examination is after radiation therapy.

Despite these and other limitations, the group should be complimented on designing and completing a prospective randomized trial in locally advanced prostate cancer. The study indicates that 3 months of androgen deprivation is beneficial in men with T2b-T4 prostate cancer who receive external beam radiation therapy. It is likely that the mechanism has something to do with an increase in tumor cell death before and during radiation, since the benefit is evident many months following the discontinuation of androgen deprivation. Unfortunately, the relapse rate is still above 50%, indicating substantial room for improvement.

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